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Clinical experience with oral lacosamide as adjunctive therapy in adult patients with uncontrolled epilepsy: A multicentre study in epilepsy clinics in the United Kingdom (UK)

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ABSTRACT

Introduction: Lacosamide (LCS) is a new antiepileptic drug (AED) licensed in the European Union (EU) and United States (US) in 2008.
Aims: To evaluate the efficacy and tolerability of add-on LCS in an out-patient epilepsy clinic setting to obtain useful information for everyday practice.
Methods: We pooled data retrospectively from the case note of patients with refractory epilepsy in whom LCS had been prescribed in 19 hospitals across the United Kingdom.
Results: Four hundred and three patients were included (mean age 41.9 years, 50.6% women, 18.1% with learning disabilities (LD)). Mean follow-up (FU) was 11.6 months (range one day to 42 months). Most patients (86.9%) presented with symptomatic partial epilepsy (SPE) and 80% were taking two or more antiepileptic drugs (AEDs) when LCS was added (mean 2, range 0–4). Retention rates were 80% at six months, 68% at one year and 45% at two years. The efficacy of LCS was evaluated at three months and at the final FU. At three months one hundred and eight patients (31.1%) reported ≥50% seizure reduction and 32 (9.2%) were seizure free. At the final FU 102 (37.5%) reported ≥50% seizures reduction and 28 (9.8%) were seizure free.

One hundred and ninety three patients (48.7%) reported adverse effects (AEs). The most frequent were sedation and dizziness, followed by nausea. Lacosamide was discontinued in 150 patients (38%), 60 due to AEs alone.
Conclusion: LCS appears to be an effective and safe AED when used as adjunctive therapy in patients with refractory partial epilepsy.

1. Introduction

Lacosamide (LCS) is a new adjunctive drug licensed for the treatment of focal seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older. Lacosamide was approved in the member states of the European Union in September 2008 and in the United States in October 2008. Lacosamide has a novel mechanism of action producing selective enhancement of sodium channel slow inactivation.[1] In addition to the treatment of epilepsy, LCS has also been found to be useful in the treatment of pain in diabetic neuropathy.[2]

Three randomised, multicentre, double blind, placebo-controlled trials of LCS have shown a major reduction in seizure frequency at three different doses with responder rates ranging from 32.7% to 35% for 200 mg/day, 38.3% to 41.1% for 400 mg/day and 38.1% to 41.2% for 600 mg/day. With placebo the responder rates in those studies ranged from 18.3% to 25.8%.[3–5] Four post-marketing studies have been published, including one from the United Kingdom (UK), showing a high response rate and good tolerability.[6–9] We present the clinical experience with lacosamide

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in 403 patients from nineteen centres in the UK, the largest post marketing group studied to date.

2. Methods

Data were obtained from the case notes between August 2010 and August 2011 from nineteen hospitals across the UK. Identification of patients and collection of data were coordinated from two sites in Leeds ($N = 287$) and London ($N = 116$). The same data collection sheet was used at both centres and the principal outcomes were based on the combined data. At the London centre more detailed information on concomitant medication and drug changes during the course of the study were also available and a further analysis relating to drug combinations was carried out in this subgroup. Both sites recruited cases from specialist epilepsy centres and the two groups of patents did not differ in terms of clinical features or outcomes. Cases were identified through electronic medical and pharmacy records of patients who had been prescribed LCS. Patients included were adults attending their usual specialist epilepsy clinic appointments and the decision to use LCS was based on the treating clinician's recommendation. Data were obtained by reviewing medical notes and electronic clinical letters. An electronic database was set up.

All patients in whom lacosamide have been prescribed were included even if they took the drug for a short period of a few days. The only exclusion criteria was the lack of follow up. Data included: demographic details such as age and sex, clinical features such as the presence of LD, epilepsy syndrome, seizure types and frequency, drug details: concomitant and previous AEDs, any change in other AEDS while on LCS, maximum doses of LCS, length of exposure to LCS, adverse effects (AEs) and withdrawal rates.

Patients were usually seen in clinic every 3–6 months. Frequency of seizures was obtained directly from what was recorded in the medical notes, or seizure diaries. Providers usually documented the number of seizures each month or recorded an average per month since the last time they saw the patient. If the numerical change in seizures was not recorded then those that improved were assessed as having less than 50% reduction in seizure frequency.

Outcome following treatment was defined and determined as follows.

Seizure free: terminal remission of 3 months or more.

50% or more reduction: a reduction in frequency of seizures of 50% or more in the last 3 months of follow-up compared to a retrospective 3 month baseline. Only cases where seizure frequency was accurately recorded were placed in this group.

Less than 50% reduction: a reduction of between 1 and 49% in the last 3 months of follow-up compared to a 3-month baseline. A minority of cases recorded as having a qualitative improvement but specific numbers of seizures were not recorded were also placed in this group.

No response and worsening of seizures: this was most often based a qualitative or overall clinical assessment from clinic letters rather than numerical measurements of seizure frequency.

Two response rates were determined. The first was based on the seizure frequency in the first three months after commencing LCS; the second on that in the three months prior to the latest follow-up. The second response rate was only determined for those patients with a minimum of six months FU. Retention time on LCS was estimated using Kaplan–Meier survival curves and Chi-square proportion tests were applied.

3. Results

A total of 403 patients who had at least one follow up were included. Gender distribution was roughly equal (males 199, females 204) with age ranging between 17 and 82 years (mean 41.9). Three hundred and seventy two were classified symptomatic or cryptogenic partial epilepsy, 13 idiopathic generalised epilepsy, 7 symptomatic generalised epilepsy and 11 were unclassified. The mean number of concomitant AED was 2.29, range 0–4; 80% of patients were taking two or more (Table 1). Learning disability (LD) was present in 73 (18.1%).

The initial daily dose of LCS varied between 25 mg and 200 mg, 50 mg/day being the most frequent (70%) with variable weekly or two weekly increments and a target tailored to each patient according to clinician judgement. The mean maximum dose was 279.4 mg/day, ranging from 25 to 700.

3.1. Follow-up and outcome

The length of exposure to LCS ranged from one day to 42 months with a mean of 11.6 months. Retention time, defined as the probability of remaining on treatment with LCS, was assessed using Kaplan–Meier survival curves (Fig. 1). The probability of remaining on LCS for all patients was 80% at six months, 68% at one year, 58% at 18 months and 45% at two years. In patients with LD, these figures were 78% at six months, 63% at one year, and 45% at 18 months and two years.

The first outcome was measured at three months FU. Of the initial 403 patients identified 46 (11.4%) had already discontinued LCS, mainly due to AEs, and ten had less than three months of exposure by the end of the study. Thus, 347 (86.1%) could be included in the analysis. Of these, 108 (31.1%) reported $\geq$50% reduction of seizures, including 32 (9.2%) SF; 98 (28.2%) had less than 50% of reduction; 50 (14.4%) had an increase in seizures; 91 (26.2%) were unchanged (i.e. no response) (See Table 2).

The second outcome was based on the seizure frequency in the last three months of follow-up. The mean FU was 15 months (range 6–42). Among 285 patients with more than six months follow-up, 102 (35.7%) had $\geq$50% reduction in seizures, of whom 28 (9.8%) were SF; 62 (21.7%) had a reduction of less than 50%, 53 (18.6%) had an increase in their frequency of seizures and 68 (23.8%) did not respond. Most patients who were initially seizure free were seizure free for the last three months. Two patients were seizure free for seven months, one for nine and one for 15. Three patients who underwent surgery for their epilepsy reported being seizure free postoperatively; two had reported less than 50% reduction of seizures while on LCS before surgery, and one had not responded to LCS before surgery.

Patients with LD had a slightly lower response rate at $\geq$50% reduction of seizures and rates of SF at final FU than patients without LD, but this difference was not significant: 32.7% compared to 36.5% (Chi-squared = 0.048, $p = 0.8272$), and 5.4% versus 10.8% (Chi-squared = 0.741, $p = 0.3894$) respectively.

The efficacy of LCS was also assessed in three seizures types: GTC, CPS, and SPS. The highest seizure reduction and seizure freedom rates were seen in tonic clonic seizures (see Tables 2 and 3).

At three months follow-up the mean maximum dose of LCS in responder patients ($\geq$50% reduction of seizures) was 291.4 mg/day (range = 100–700), in seizure free patients was 256.5 mg/day (range = 100–400), in partial responder patients was 314.1 mg/day (range = 25–600) and in non-responder patients was 295.6 mg/day (range = 50–650). At the final follow-up these doses were 310.8 mg/day (range = 100–700), 251.8 mg/day (range = 100–450), 322.3 mg/day (range = 100–600) and 304.2 mg/day (range = 100–600), respectively.

3.2. Adverse effects and withdrawal

Adverse effects were reported in 193 (48.7%) patients. The most frequent were sedation in 89 patients, dizziness in 73, nausea and

Table 1
Clinical features of all 403 patients and outcome at final follow up in 285 patients with 6 months of more follow-up.

Characteristic	Total number/number with ≥6 months FU	Outcome of seizures at the last FU (285 patients with ≥6 months FU)				
		>50% reduction including SF patients	<50% reduction	Patients seizure free	Non responder	Increase
		N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Age						
17–30	98/68	22 (32.4)	16 (23.5)	4 (5.8)	16 (23.5)	14 (20.6)
31–50	202/143	50 (34.9)	30 (20.9)	14 (9.7)	36 (25.1)	27 (18.9)
51–82	103/74	30 (40.5)	16 (21.6)	10 (13.5%)	16 (21.6)	12 (16.2)
LD						
Yes	73/55	18 (32.7)	13 (23.6)	3 (5.4)	13 (23.6)	11 (20)
No	330/230	84 (36.5)	49 (21.3)	25 (10.8)	55 (23.9)	42 (18.2)
Gender						
Male	199/148	51 (34.4)	28 (18.9)	12 (8.1)	31 (20.9)	38 (25.6)
Female	204/137	51 (37.2)	34 (24.8)	16 (11.6)	37 (27)	15 (10.9)
Syndrome						
IGE	13/9	3 (33.3)	1 (11.1)	3 (33.3)	3 (33.3)	2 (22.2)
SGE	7/5	3 (60)	1 (20)	0 (0)	0 (0)	1 (20)
SPE	372/263	94 (35.7)	58 (22.1)	24 (9.1)	64 (24.3)	47 (17.8)
UC	11/8	2 (25)	2 (25)	1 (12.5)	1 (12.5)	3 (37.5)
Concomitant drugs						
1	83/51	19 (37.2)	12 (23.5)	6 (11.7)	13 (25.5)	7 (13.7)
2	158/117	47 (40.1)	27 (23.1)	11 (9.4)	28 (23.9)	15 (12.8)
3+	162/117	36 (30.7)	23 (19.6)	11 (9.4)	27 (23.1)	31 (26.4)
Exposure to LCS/months						
<3.0	56					
3.0–5.9	62					
6.0–11.9	96	26 (27.1)	16 (16.6)	10 (14.4%)	33 (34.3)	21 (21.8)
12.0–17.9	94	35 (37.2)	19 (20.2%)	11 (11.7%)	24 (25.5)	16 (17)
18.0–23.9	57	24 (42.1)	17 (29.8%)	3 (5.3%)	8 (14)	8 (14)
>24.0	38	17 (44.7)	10 (26.3%)	4 (10.5%	3 (7.8)	8 (21)
All cases	403/285	102 (35.7)	62 (21.7)	28 (9.8%)	68 (23.8)	53 (18.5)

FU, follow-up; LD learning difficulties; IGE, idiopathic generalised epilepsy; SGE, Symptomatic generalised epilepsy; UC, unclassified.

other gastrointestinal disturbances in 56, unsteadiness in 43, double or blurred vision in 42, headache in 32, and skin irritation in 13. Other less frequent side effects are listed in Table 4.

One hundred and fifty (38%) patients out of 403 discontinued LCS. The average retention time in those patients was 7.2 months. Of those 150 patients, 84 (20.8%) withdrew mostly due to intolerable AEs, 35(8.7%) due to lack of efficacy only, 10 (2.5%) due to increase in seizure frequency and 10 (2.5%) because of increase in seizure severity. In 11 (2.7%) the cause was not stated. Of the 84 patients with intolerable AEs, four also had increased seizure frequency and 20 lack of efficacy. The most frequent AEs in those patients withdrawing LCS were somnolence, dizziness, unsteadiness, double vision, headache, nausea, other gastrointestinal disturbances and increase in seizure frequency.

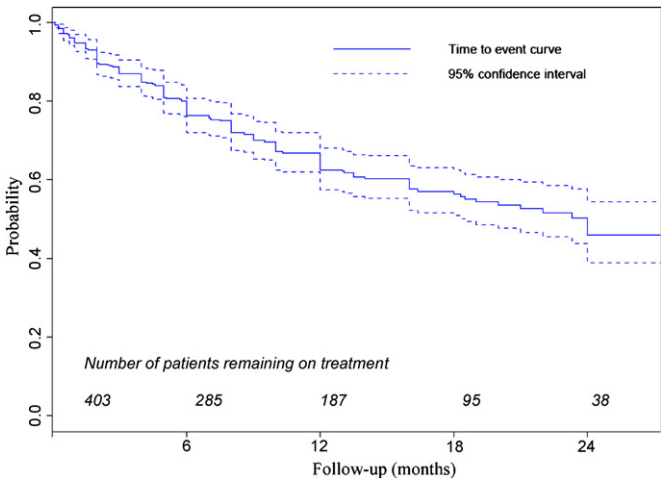

Fig. 1. Actuarial probability of remaining on treatment with lacosamide.

Patients with LD presented less AEs than those without LD but a higher proportion of patients with LD underwent LCS withdrawal, mainly due to AEs and inefficacy of the drug. However, no significant differences were found comparing those variables (Chi-squared = 0.213, $p = 0.6465$ and Chi-squared = 0.005, $p = 0.9416$, respectively).

3.3. Idiopathic generalised epilepsy

Thirteen patients with IGE received LCS. Epilepsy in these patients was highly refractory, they were taking 2.6 AEDs (range 1–4) on average before starting LCS. The average maximum dose of LCS was 280 mg/day (range = 100–400). Three patients had a ≥50% seizure reduction at an average dose of 200 mg/day. One of these patients, followed for 27 months, reported a few seizures on some days with long seizure free periods. Another patient, taking in addition levetiracetam, clobazam and phenytoin before starting LCS and followed-up for 8 months, reported no seizures during that period. Five patients did not experience any change in seizure frequency, and two had increased seizure frequency. Four patients stopped LCS, 1 for SEs, 1 because of increasing myoclonic jerks and two for lack of efficacy.

3.4. Concomitant sodium channel medication

In a subgroup of 116 patients from one centre the outcome at the final FU was compared in patients taking LCS plus another sodium channel drug verses patients taking LCS plus AEDs with a different mechanism of action. We also looked for any reduction or withdrawal of concomitant medications in all patients that presented some degree of improvement.

The mean age in this group was 41.3 years (range = 17–74); 65 were female; the mean duration of epilepsy was 27.1 years; most had SPE (92.2%). the mean FU was 10.1 months; 72% had tried at

Table 2
Seizure outcome at 3 months of follow up.

Seizure type	Baseline to 3 months/patients with at least 3 months FU (347) *N*%				
	≥50% reduction including SF patients	≤50% reduction	Seizure free	No response	Increase in seizures
All seizures	108 (31.1)	98 (28.2)	32 (9.2)	91 (26.2)	50 (14.4)
TCS (127)	58 (45.7)	20 (15.7)	30 (23.6)	36 (28.3)	13 (10.2)
CPS 268	90 (33.8)	60 (22.6)	31 (11.7)	82 (30.6%)	36 (13.4)
SPS (43)	12 (27.9)	8 (18.6)	5 (11.6)	19 (44.2)	4 (9.3)

Table 3
Seizure outcome at 6 months of follow up.

Seizure Type	Baseline to final 3 months follow up/patient with at least 6 months FU (285) N(%)				
	≥50% reduction includimng SF patients	≤50% reduction	Seizure free	No response	Increase in seizures
All seizures	102(35.7)	62(21.7)	28(9.8)	68(23.8)	53(18.6)
TCS (107)	47(43.9)	15(11.8)	22(20.6)	30(28)	15(14)
CPS (221)	91(41.1)	36(16.2)	31(14)	56(25.3)	38(17.2)
SPS (34)	11(32.3)	9(26.4)	6(17.6)	10(29.4)	4(11.7)

TCS, tonic clonic seizures; CPS, complex partial seizures; SPS, simple partial seizures.

least four AEDs and 71.5% were taking two or more AEDs as LCS was commenced. The most frequent AEDs were: carbamazepine (CBZ) 49, levetiracetam (LEV) 48, clobazam (CLB) 32, sodium valproate (SV) 22, lamotrigine (LMT) 20, topiramate (TPM) 16, and phenytoin (PHT) 14.

Of these 116 patients, 74 were taking at least one-sodium channel blocker (PHT, CBZ, oxcarbazepine or LMT). There were no significant differences in the incidence of AEs or of withdrawal of LCS in the group taking LCS plus another sodium channel blocker in comparison to LCS plus an AED with a different action (AEs: 24/74 cf. 12/42, Chi-squared = 0.013, $p = 0.9081$; withdrawal: 22/74 cf. 11/42, Chi-squared = 0.010, $p = 0.9218$).

Regarding efficacy analysis, patients on sodium channel drugs were more likely to have ≥50% seizure reduction and become seizure free than the patients taking other combination of drugs, but this difference was again not significant; 26/74 compared to 11/42(Chi-squared = 0.273, $p = 0.6013$), and 15/74 versus 3/42 (Chi-squared = 1.863, $p = 0.1722$), respectively (see Table 5). Of 54(46.5%) patients reporting some degree of improvement in this group, 12(22.2%) had reduction of other drugs, 2 reduced carbamazepine and 2 reduced phenytoin. Six (11.1%) discontinued other medications: 2 levetiracetam, 2 zonisamide, 1 sodium valproate and 1 tiagabine. None was moved to monotherapy (see Table 6). Additionally 7 (6%) patients reported improvement in seizure severity without improvement in seizure frequency.

Table 4
Incidence and nature of side effects.

Side effect	Total
Sedation/somnolence	89
Dizziness	73
Nausea/gastrointestinal disturbances	56
Unsteadiness	43
Double/blurred vision	42
Headache	32
Skin irritation	13
Weight gain	7
Mood change	6
Confusion/mentally slow	6
Hallucinations	5
Sleep disturbance	5
Slurred speech	5
Pins and needles/numb fingers	4
Memory problems	4
Tremor	3
Depersonalisation/abnormal thoughts	3
Limbs/joints pain	3
Behaviour/verbal aggression	2
Breathless	2
Leg oedema	1
Weakness	1
Reduce appetite	1
Myoclonic jerks	1
Muscle spasm	1
Drooling	1

4. Discussion

This study reflects the experience with LCS in 403 patients with uncontrolled epilepsy in an outpatient setting in 19 hospitals in the UK and is the largest observational study reported. The patient population in this project differs from the pivotal studies and other retrospective and prospective audits in that outcome was assessed using retention times and we included all patients in whom LCS had been prescribed and not only those with partial onset seizures. The study was a retrospective chart review. It was not always possible to determine the outcome on the basis of exact measures of seizures numbers. Cases were only recorded as seizure free or having a 50% plus response if numbers or frequency of seizures were clearly recorded. Qualitative outcomes such as improved were assumed to have had only a partial response of less than 50%. Assessments of no change or worsening were more often based on overall clinical assessments. Although the same proforma for data collection was used at each site, a prospective evaluation of adverse events, including cardiac symptoms or abnormalities in ECG, was not performed which may have led to these being underestimated. All cases were however being followed by specialist epilepsy services and it is unlikely that major or important adverse events were missed.

Because multiple factors effect retention time and patient samples vary, comparison with previous studies is difficult. These results however are broadly in line with three large studies that have assessed multiple drugs including topiramate, levetiracetam and zonisamide in large populations.[10–12] Lower retention times of 23% at one year have been reported for gabapentin probably reflecting lesser efficacy of this drug as an add on in chronic epilepsy.[10] The higher retention rates of around 75% reported for lamotrigine [11,12] may be due to the increasing use of this drug as a long term first line medication substituted for other drugs such as phenytoin or carbamazepine. It is always best therefore to combine

Table 5
Outcome at the last FU in 116 patients taking or not taking concomitant sodium channel drugs.

Characteristic	*N* = 116	Side effects	Withdraw	≥50% seizures reduction final FU	Seizure free final FU
Taking sodium channel drugs (PHT, CBZ, OXC, LMT)	74	24 (32.4%)	22 (29.7%)	26 (35.1%)	15 (20.2%)
Taking other drugs	42	12 (28.5%)	11 (26.1%)	11 (26.1%)	3 (7.1%)

Table 6
Change in concomitant drugs in 54 of 116 patients that improved (116 patients in whom full AED data were available).

Drug	Reduced	Removed
Carbamazepine	2	
Phenytoin	2	
Sodium valproate	1	1
Tiagabine	1	1
Lamotrigine	1	
Levetiracetam	1	2
Phenobarbitone	1	
Clobazam	1	
Primidone	1	
Zonisamide	1	2
Total	**12**	**6**

assessment of retention times with a detailed description of the effects on seizure control and adverse events.

Our finding of a response rate at the final FU of 35.7% was consistent with three pivotal LCS trials which found a median percentage of patients with ≥50% seizure reduction of 33.3–34.1% at LCS 200 mg/day, 36.8–39.7% at 400 mg, and 39.6% at 600 mg.[3–5,13] Our response rate of 32% was also similar to that observed in a post-marketing study.[6] One retrospective study found a 47% response rate but included only 60 patients.[7] The proportion of patients becoming SF at the last FU in our study was 9.8% (mean maximum dose 252 mg/day) and greater than 2.4–8% found in previous studies (mean dose 200–600 mg/day).[4,5] However, a study in Scotland found 26% of patients to be SF (median dose 100 mg/day; range 50–300) for a six months period.[8] In this study the response rate was particularly high in patients using LCS as a first add on medication. The seizure freedom rates in this study are similar to those previously reported with LEV suggesting good efficacy.[11] Moreover, the average maximum dose of LCS in those responder patients and those reaching freedom of seizures at the last FU was reasonably low: 293 mg/day and 239 mg/day respectively compared to those in the pivotal studies and similar to other post-marketing published studies.[7,9] It is usually the practice of UK Consultant Neurologists, particularly in patients on multiple drugs, to titrate slowly and observe the response.

Forty nine percent of patients presented at least one adverse effect which is higher than most published studies, except for one post-marketing study that reported a rate of 52%.[6] The most commonly experienced AE in previous controlled and post-marketing studies was dizziness, followed by nausea, and vomiting.[4,6–8,11,12] In our population sedation was the most frequent adverse effect, which occurred in 89 patients, followed by dizziness in 73, and gastrointestinal disturbances in 56. Several side effects not reported in pre-marketing studies were found in this and other post marking trials[6,8] which could be due to the larger population studied. These included skin irritation, weight gain and limb pain. Some neurological and neuropsychiatric side effects were also reported: paraesthesia, sleep disturbance, slurred speech, memory problems, tremor, mood change, confusion and slowness of thinking, hallucinations, depersonalization/abnormal thoughts, and behaviour problems. In keeping with previous pivotal studies, audits and service evaluations, the overall incidence of major neuropsychiatric disorders such as depression and psychosis appeared to be low, in keeping with the experience seen in other drugs known to act through the sodium channel. Cardiac arrhythmias were not reported in the medical notes in any case.

One hundred and fifty patients (38%) discontinued LCS, most of them (60%) within six months, mainly due to AEs of sedation and dizziness. Our rates of discontinuation are considerably higher than other studies that reported 12.4%[8] and 21%,[9] 28%.[6] There is evidence that combining AEDs that act on sodium channels may be more likely to produce AEs in comparison to combining AEDs with different actions.[14–17] Novy et al. reported seven patients who experienced significant AEs following the addition of LCS to other sodium channel blocking AEDs, and suggested that this was probably due to pharmacodynamic interaction.[14] They discussed the possibility of reducing existing sodium channel blocking AEDs before introducing LCS to reduce the incidence of AEs. In general, prospective reduction of concomitant sodium channel co-medications was not undertaken in our study, which might have influenced the results.

It has been suggested that combinations of AEDs with different mechanisms of action might be more efficacious and/or well tolerated in comparison to combinations including AEDs with similar mechanisms of action. This remains an attractive hypothesis on which to attempt to base rational polytherapy. This was lent some support by a post-marketing study and an analysis that pooled data from the pivotal LCS studies that found higher response rates where LCS was combined with non-sodium channel AEDs.[9,18] In our study adding LCS to drugs acting on the sodium channel was in general more efficacious compared to adding it to drugs with other mechanisms of action but the findings were not statistically significant. Both studies were not designed to examine this question which would require balancing of clinical features in both treatment groups. Our study did not confirm the notion that LCS is more efficacious and better tolerated when combined with non sodium channel agents.

Almost 20% of the patients in this study had LD. The retention rate of LCS was slightly lower in this group at six months and one year but at 18 months and two years this rate become similar to that of patients without LD. The two year figure was comparable to that found for LEV in a previous study with a population of similar characteristics.[19] In our study, AEs and reasons for withdrawing LCS were similar in patients with or without LD. Behavioural side effects were rare or absent.[20] Results from several clinical trials have shown LCS to be effective for the treatment of partial onset seizures, but there are no studies in patients with IGE. We found that 13 patient with IGE were prescribed LCS. Three of these responded with two presenting long periods of seizure freedom. It is not possible to draw conclusions regarding any role for LCS in IGE from our findings other than that it is worthy of further investigation.

In conclusion, the results from this study show that LCS is a safe and effective drug when given as adjunctive therapy in partial-onset seizures in the general population of patients with epilepsy and in those with intellectual disabilities.

Conflict of interest

This study was supported by an unrestricted donation from UCB UK. Dr Elwes has received previous unrestricted research grants from UCB and served on the Medical Advisory Board for UCB.

Dr Flores has received sponsorship from UCB to attend conferences. Dr Kemp has received sponsorship to attend conferences from pharmaceutical companies including UCB. Ms Colbeck has received sponsorship from UCB to attend a conference. Dr Nashef has been supported to attend conferences by pharmaceutical industry. Dr Moran has received sponsorship from UCB to attend conferences. Dr von Oertzen has received research grants from UCB, served on medical advisory board for UCB and received sponsorship for conferences from UCB.

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